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P.I. Robert E Reiter

INTRODUCTION

PSCA is a cell surface antigen expressed in normal prostate, which was previously shown by our group to be overexpressed (when compared to expression in normal prostate) in a significant percentage (30-40%) of prostate cancers. Our initial analysis suggested that PSCA expression might be higher in tumors of higher Gleason score and stage and in bone metastases. The major goal of the current proposal was to establish prostate tissue arrays and test the hypothesis that PSCA expression could be used prognostically. We also wanted to see if PSCA could identify patients who might be candidates for anti-PSCA antibody therapy. Finally, we wanted to ask whether PSCA expression in bone marrow could identify patients at high risk to recur after initial therapy with prostatectomy.

PROGRESS REPORT

Specific Aim 1: To test the prognostic significance of PSCA overexpression in patients with clinically localized prostate cancer.

Task 1. PSCA in tissue arrays. The major focus of our work over the past year has been to finish construction of prostate cancer tissue arrays and to stain these in order to determine the correlation of PSCA with clinicopathologic factors. We initially constructed an array containing tissue cores from 250 patients who had undergone radical prostatectomy and for whom we constructed a clinical database. Over the past year, we have constructed a second array containing an additional 245 patients with localized prostate cancer, as well as a small number of lymph node metastases and cases of prostate intraepithelial neoplasia. This array includes a single core of normal prostate adjacent to three cores from the associated cancer in order to account for tumor heterogeneity.

With arrays now in hand, we have completed staining of all arrays. Representative staining is shown in Figure 1, below. We are currently in the process of reading these arrays and scoring them. We should note that construction of arrays and, more importantly, establishment of correct parameters for staining, has taken up the bulk of the year. Initial staining using parameters established on whole sections did not work. It turns out that arrays are more difficult to stain, and that each antigen behaves differently. This is the principle reason we went back and made the second array, since staining of our initial array was suboptimal. We have now optimized the staining parameters and are in the process of scoring the slides. We expect to complete this major part of our project over the next 6 months.
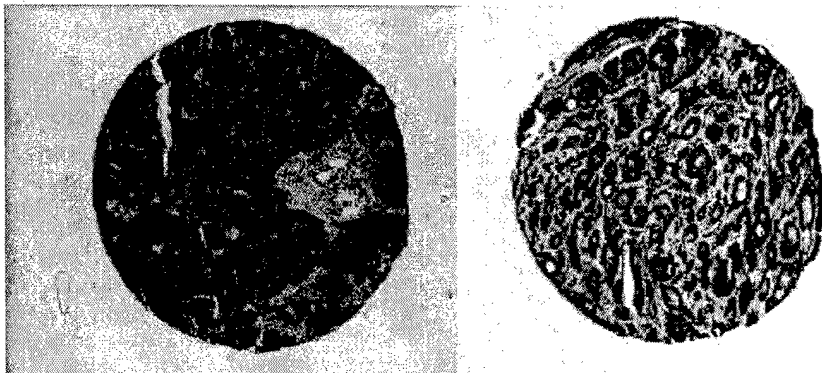
Figure 1. Example of two tumor cores from the UCLA tissue array (#2), showing staining for PSCA in both a high-grade tumor (Gleason 5+4; left) and moderate grade tumor (Gleason 3+3; right)

Task 2: MYC/PSCA gene amplification: In collaboration with Dr. Robert Jenkins at Mayo clinic, we will perform FISH analysis for MYC and PSCA in order to determine the frequency of gene amplification and the relationship between the two genes. FISH analysis is underway at Mayo, following which we will stain the same arrays for PSCA protein expression.

Task 3: PSCA in biopsies and matched prostatectomies. 50 paired biopsy and prostatectomy specimens have been collected retrospectively. We will assemble additional pairs over the coming year and will stain them for PSCA in order to determine the correlation of biopsy and prostatectomy staining.

Specific Aim 2: Prognostic significance of PSCA in blood and bone marrow samples. We have continued to develop appropriate assay using magnetic bead technology and plan to begin to collect bone marrow biopsies once we have obtained IRB approval from the DOD. The UCLA IRB approved our consent and proposal, but we still need to address a number of issues to the DOD IRB. The major stumbling block was that the DOD IRB did not believe there was sufficient preliminary data to justify obtaining bone marrows from patients at the time of prostatectomy. We believe completion of Aim 1 will address this issue. In addition, a Japanese group recently published a paper showing that the presence of PSCA-expressing cells ion peripheral blood of patients with prostate cancer was a sensitive and highly specific predictor of prostate cancer survival[1]. We continue to think PSCA expression in blood and bone marrow will have valuable prognostic significance.

We should note that we have obtained from Dr. Robert Vessella at the University of Washington, bone specimens of 10 patients who died from prostate cancer, and are staining these. In addition, in collaboration with his group, we are assaying for PSCA expression by RT-PCR in bone marrow aspirates of patients with localized and locally advanced disease. For logistical reasons, these assays are being completed in Seattle. Finally, we have obtained tissue arrays from Dr. Mark Rubin at Dana Farber Cancer Center containing a large number of tumors from autopsy-obtained androgen independent cancers. These have already been stained and will be read over the coming year.

KEY RESEARCH ACCOMPLISHMENTS OVER YEAR 1:

1. Construction of multiple tissue arrays of localized prostate cancer.

2. Establishment of antigen retrieval and staining techniques specific for arrayed specimens.

3. Completion of PSCA staining.

4. Established collaborations with Drs. Rubin (androgen independent tissue arrays), Dr. Vessels (bone marrow aspirates), and Dr. Jenkins (FISH analysis).

CONCLUSION

We have made progress towards defining whether or not PSCA has prognostic value. These studies should be completed over the coming year. We hope to have preliminary data regarding the utility of PSCA expression in bone marrow aspirates and to begin a prospective trial testing this hypothesis over the coming year.

1. Hara, N., Kasahara, T., Kawasaki, T., Bilim, V., Obara, K., Takahashi, K., and Tomita, Y. Reverse Transcription-Polymerase Chain Reaction Detection of Prostate-specific Antigen, Prostate-specific Membrane Antigen, and Prostate Stem Cell Antigen in One Milliliter of Peripheral Blood: Value for the Staging of Prostate Cancer. Clin Cancer Res, 8: 1794-1799, 2002.